Asymmetric Catalysis

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Palladium-Catalyzed Asymmetric Reductive Heck Reaction of Aryl Halides**

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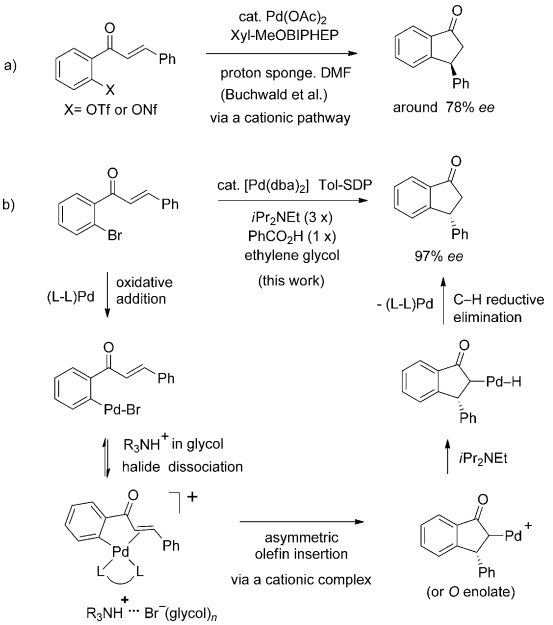
Abstract: *Asymmetric reductive Heck reaction of aryl halides is realized in high stereoselectivity. Hydrogen-bond donors, trialkylammonium salts in a glycol solvent, were used to promote halide dissociation from neutral arylpalladium complexes to access cationic, stereoselective pathways.*

In the 1980s, Cacchi et al. reported that aryl halides reacted with enones and enals to form conjugate adducts in the presence of palladium catalysts.[1] Alkyl amines and formates were the hydride source in the process.[2] Typically, neutral or anionic aryl–Pd complexes were used and electron-poor olefins and styrene were preferred olefin substrates for insertion.[3] As a common feature, the key aryl–Pd species were coordinatively saturated by ligands (phosphines, N-heterocyclic carbenes, halides, and acetates). This saturation successfully helps to out-compete undesirable β-hydride elimination processes.[4] This reaction was used in racemic syntheses of drug candidates, and for many years an enantioselective version was unavailable.[5] In comparison, metal-catalyzed conjugate additions using Cu,[6] Rh,[7] or Pd[8] catalysts also afforded the same sets of conjugate adducts, but they needed to use organometallic reagents, the latter often being made from aryl halides.[9]

Previously, Buchwald et al. initiated the study of asymmetric reductive Heck reactions using aryl triflates and nonaflates, and intramolecular insertion into enones gave moderate *ee* values in most examples (Scheme 1 a).[10] Herein, we report reductive Heck reaction of aryl halides to provide 3-arylindanones in high *ee* values (Scheme 1 b). These chiral compounds are used in the synthesis of indatraline (antidepressant), tefludazine (antipsychotic), and tolterodine for the treatment of urinary disorders.[11] Today, a dozen asymmetric methods are available to access chiral indanones,[12] but a general method to access 3-arylindanones is still lacking.[13]



Scheme 1. Comparison of two reductive Heck reactions. DMF = *N*,*N*-dimethylformamide, Tf = trifluoromethanesulfonyl.

Asymmetric 1,4-addition of organometallic reagents to indenone is often out-competed by 1,2-addition.[14]

Initially, we used (*E*)-*o*-bromochalcone in a model study, and it was easily prepared from an aldol condensation of a methyl ketone and benzaldehyde (Table 1). After many trials, we found that spiro-di(1,1′-indanyl)bisphosphine (SDP) afforded excellent *ee* values (entries 1–3). The SDP ligands were pioneered by Qi-Lin Zhou and have found widespread applications in asymmetric metal catalysis.[15] BINAP, DM-SEGPHOS, and Xyl-MeO-BIPHEP gave 35–77% *ee* (entries 4–9). Bisphosphine oxides and phosphine oxazolines (Pfaltz's PHOX) were found to be catalytically inactive (entries 10–12).

A 1:3 molar combination of benzoic acid and iPr$_2$NEt were used to form an alkylammonium salt in situ during reaction. The latter was used to ionize the arylpalladium halide by hydrogen bonding, in a glycol solvent (Table 2). The excess alkylamine was needed for formation of palladium hydride and regeneration of the active catalyst. When benzoic acid was omitted, both the yield and *ee* value decreased significantly (Table 2, entry 1).

Previously Xiao et al. reported that alkylammonium salts or a glycol solvent facilitated halide dissociation in regioselective Heck reactions.[16] We found that both R_3NH^+ salts and glycol were needed in our study of the asymmetric Heck

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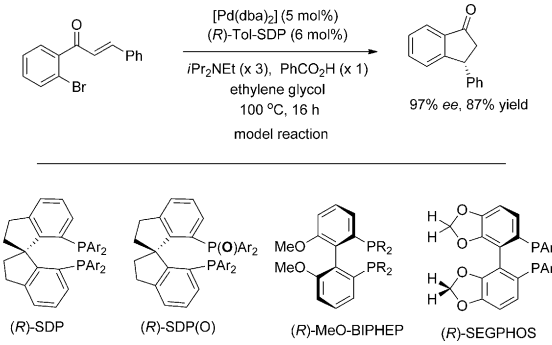
Table 1: The effect of chiral bisphosphines (GC conversion and calibrated GC yield).



Entry	Chiral ligands	Conv. [%][a]	Yield [%][a]	*ee* [%][b]
1	(*R*)-SDP	100	93	97
2	(*R*)-Tol-SDP	100	87	97
3	(*R*)-Xyl-SDP	100	43	69
4	(*R*)-BINAP	50	35	−60
5	(*R*)-DM-Segphos	75	68	−54
6	(*R*)-DTBM-Segphos	0	0	–
7	(*R*)-MeO-BIPHEP	25	20	−71
8	(*R*)-*i*Pr-MeO-BIPHEP	100	78	−81
9	(*R*)-Xyl-MeO-BIPHEP	65	61	−77
10	(*R*)-BINAP(O)	0	0	–
11	(*R*)-Xyl-SDP(O)	0	0	–
12	(*R*)-*i*Pr-PHOX	0	0	–

[a] Determined by GC. [b] Determined by HPLC on a chiral stationary phase. dba = dibenzylideneacetone.

Table 2: Optimization of reaction conditions for the model reductive Heck reaction.

Entry	Change of conditions	Conv. [%][a]	Yield [%][a]	*ee* [%][b]
1	no BzOH	100	36	55
2	AcOH instead of BzOH	100	80	91
3	CF_3CO_2H	100	91	97
4	AgOTf instead of BzOH	100	45	58
5	Ag_2CO_3	90	38	74
6	$ZnCl_2$	100	55	76
7	$ZnBr_2$	100	51	80
8	proton sponge as base	100	93	96
9	Et_3N	100	94	95
10	DABCO	100	88	93
11	NaOAc	100	73	96

[a] Determined by GC. [b] Determined by HPLC on a chiral stationary phase. DABCO = 1,4-diazobicyclo[2.2.2]octane.

reaction of aryl halides.[17] In our DFT studies, hydrogen bonding of trialkylammonium NH and alcoholic ROH with a halide ion not only lowered the barrier, but also stabilized the ionized products.[18] Silver salts were commonly believed to remove halide ions from neutral aryl palladium halides with ease in Heck reactions.[19] However, AgOTf and Ag_2CO_3 led to poor results (Table 2, entries 4 and 5). They probably caused oxidation of phosphines. In comparison, redox-inactive zinc salts gave around 80% *ee* (entries 6 and 7). In entries 1–7 where there was a problem of material balance, and a complex mixture of unidentifiable byproducts were seen in the GC analysis. The simple byproduct from reduction

Table 3: Effect of solvents on the model reductive Heck reaction.

Entry	Solvent	Dielectric constant	Conv. [%][a]	Yield [%][a]	*ee* [%][b]	Cationic pathway
1	ethylene glycol	37	100	87	97	yes
2	EtOH	25	35	30	99	yes
3	*i*PrOH	18	55	38	95	yes
4	THF	8	100	72	0	no
5	acetone	21	70	54	11	no
6	DMA	38	100	76	5	no
7	DMF	37	100	78	86	mainly

[a] Determined by GC. [b] Determined by HPLC on a chiral stationary phase. DMA = dimethylacetamide, THF = tetrahydrofuran.

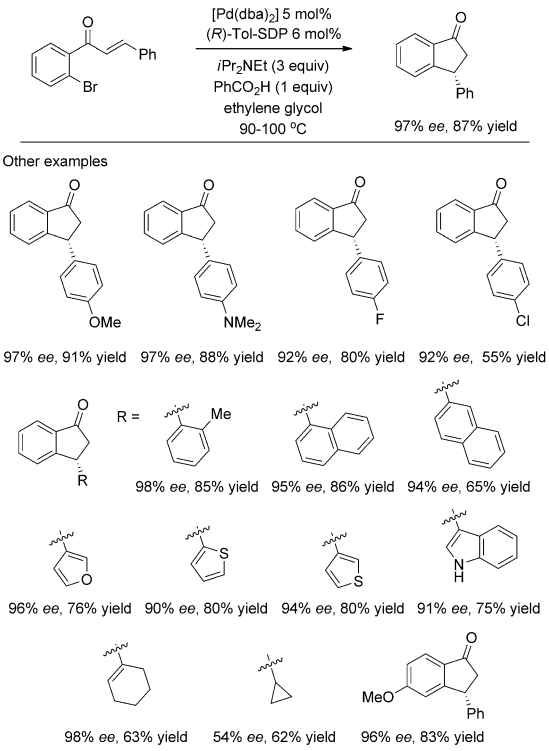
of the aryl–Br bond was not significant. Trialkylamines were the hydride source (entries 8–10), as previously reported by others.[10a,20] When NaOAc was used as the base, the glycol was the plausible hydride source (entry 11).[21]

The glycol solvent was also important to stabilize the bromide anion (Table 3, entry 1).[22] The reaction became much slower in both ethanol and isopropanol (entries 2 and 3). In THF, toluene, and acetone, almost 0% *ee* was observed. Thus, in these solvents, olefin insertion into the neutral palladium complex took place, and was non-stereoselective. A dramatic disparity was found between DMF (86% *ee*) and DMA (5% *ee*; entries 6 and 7).[23] The difference cannot be explained by high solvent polarity[24] or strong solvation of metal cations. The formyl hydrogen atom of DMF was reported to participate in hydrogen bonding between DMF molecules.[25] Thus, DMF may serve as the hydrogen-bond donor in this case, while DMA cannot.[26]

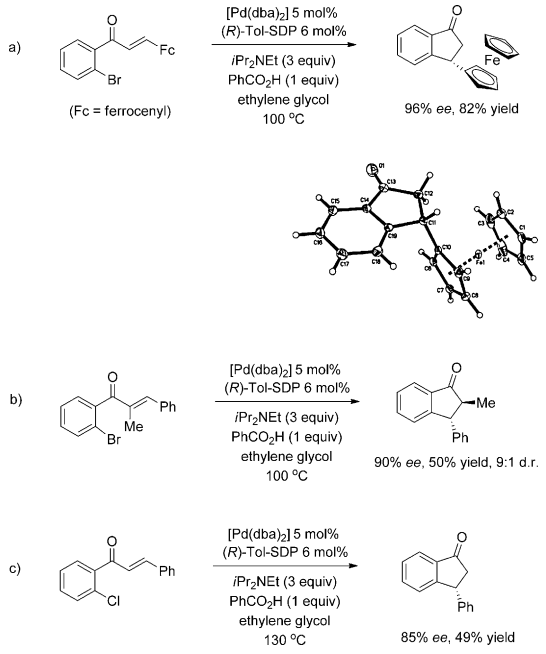
In examination of the scope of the asymmetric cyclization (Scheme 2), we chose to use Tol-SDP because it performed better than the parent SDP in cyclization of most substrates. Both electron-donating and electron-withdrawing groups can be present on β-aryl rings of chalcones. Thiophene, furan, and indole were compatible with the palladium catalysis. A β-cyclohexyl group can also be present. A β-cyclopropyl group led to 54% *ee* while other alkyl groups led to even lower selectivity.

Single-crystal X-ray diffraction of a product containing ferrocene unequivocally established the 3*S* configuration (Scheme 3a). For a chalcone carrying an α-methyl group, asymmetric cyclization gave the *trans* isomer as the major product, which is both the kinetically and thermodynamically favored product (Scheme 3b). When *ortho*-chlorochalcone was tested, the reaction did not proceed at 100 °C because of the difficult oxidative addition. At 130 °C, 85% *ee* was observed (Scheme 3c).

3-Arylindanones can be transformed into many chiral compounds (Scheme 4), which are not straightforward to make from other reactions: hydrogenolysis over Pd/C, reduction to a *cis*-alcohol with $NaBH_4$, Baeyer–Villiger oxidation oxidized to a lactone, and palladium-catalyzed α-arylation with good *trans* selectivity.[27] No *ee* erosion was observed on biarylmethine centers. Furthermore, *cis*-3-phenyl-1-indanol was readily substituted with either a thiophene ring[28] or an allyl group by *trans* addition to an indanyl cation.

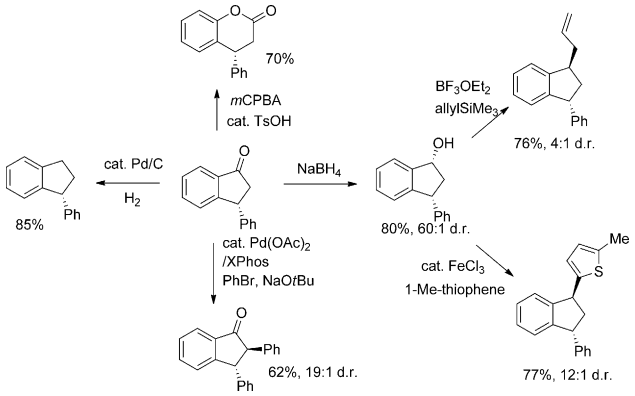


Scheme 2. Reductive Heck reaction of *ortho*-bromochalcones. Yields are those of isolated products (0.5 mmol scale).



Scheme 3. Reductive Heck reaction of other chalcone derivatives (yields of isolated products) and ORTEP of (*S*)-3-ferrocenyl-1-indanone with 50% probability of thermal ellipsoids.[34]

We then conducted DFT calculations on the stereo-determining step of aryl insertion using a cationic complex [(*R*)-Tol-SDP](*o*-chalconyl)palladium(II) (Figure 1). Several



Scheme 4. Transformation of chiral 3-phenylindane without loss in the *ee* values.

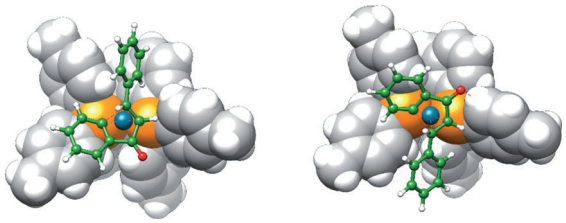


Figure 1. Transition structure TS-R (left) and lower-energy transition structure TS-S (right) for aryl insertion in cationic [(*R*)-Tol-SDP](*o*-chalconyl)palladium(II). The ligand Tol-SDP is in space-filling model and other atoms of the complex are shown as ball-and-stick model. Pd blue, P orange, O red, and C (of chalcone) green.

conclusions were drawn: a) The energy gap of two transition states was calculated to be 4.6 kcal mol^{-1}, which is consistent with observed 97% *ee* at 90–100 °C. b) The main pathway that proceeds via TS-S gives the major *S*-configured product and its insertion barrier is around 17 kcal mol^{-1}. c) No severe van der Waals contact was identified in either of the two TSs, so a simple model of steric repulsion seems implausible. d) A close examination of TS-S revealed that the ketone oxygen atom (highlighted in red) was close to a hydrogen atom of a *P*-tolyl ring. The C–H···O distance is 2.2 Å and the bond angle of C-H-O is 152°. They fall into the prescribed range for C–H···O weak hydrogen bonds,[29] and provides stabilization of around 0.5–4 kcal mol^{-1}.[30] This kind of attractive interaction was absent in TS-R. Recently, the use of aryl CH···O hydrogen bonding and other weak attractive forces have emerged in asymmetric metal catalysis.[31]

In summary, we report a reductive Heck reaction process which uses aryl halides directly to afford 3-arylindanones in high *ee* values. As a key reaction design, alkylammonium salts and glycol were used as hydrogen-bond donors to help halide dissociation under mild reaction conditions. Alkylammonium salts are routinely formed from alkylamines in asymmetric Heck reactions[32] and they may act as halide abstractors in polar solvents in, for example, Overman's Heck cyclizations.[33]

Keywords: asymmetric catalysis · hydrogen bonding · olefins · palladium · synthetic methods

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[34] CCDC 1047580 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Communications

Asymmetric Catalysis

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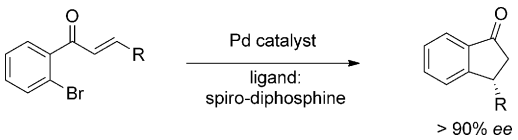

Palladium-Catalyzed Asymmetric Reductive Heck Reaction of Aryl Halides

Hydrogen-bond donors promote halide dissociation from neutral arylpalladium halides to access an enantioselective cationic pathway. The use of trialkylammonium salts in a glycol solvent enables asymmetric reductive Heck reaction of aryl halides in high stereoselectivity.